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Basal and Dexamethasone Suppressed Salivary Cortisol Concentrations in a Community Sample of Patients with Posttraumatic Stress Disorder

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Background: *Posttraumatic stress disorder (PTSD) has been associated with lower concentrations of cortisol and enhanced suppression of cortisol by dexamethasone, although discrepancies exist among reports. The objective of the study was to determine the pattern of cortisol responses in patients seeking treatment for PTSD resulting from a variety of traumatic experiences and to test whether cortisol responses are significantly related to childhood trauma, severity of symptoms, or length of time since trauma.*

Methods: *Salivary cortisol was measured at 8 AM, 4 PM, and 10 PM on 2 consecutive days before and after a 10 PM dose of .5 mg dexamethasone in 17 psychotropic medication and substance-free subjects with PTSD and 17 matched control subjects.*

Results: *Repeated-measures analysis of variance (ANOVA) of the baseline salivary cortisol concentrations demonstrated a significant effect for group with higher concentrations in the PTSD group but no significant differences in responses to dexamethasone. The presence of childhood abuse did not significantly affect salivary cortisol concentrations, and there was no correlation between predexamethasone cortisol and either the severity of PTSD symptoms or the time since the index trauma.*

Conclusions: *Neither low basal concentrations nor enhanced suppression of cortisol are consistent markers of a PTSD diagnosis.*

Key Words: Dexamethasone, HPA axis, posttraumatic stress disorder, salivary cortisol, stress, trauma

The adrenal steroid hormone cortisol has a wide range of actions in the body, including altering metabolic processes (e.g., gluconeogenesis), dampening various acute stress responses (e.g., immune activity), and altering central nervous system function (e.g., the CA3 region of the hippocampus). The presence of a persistent abnormality in cortisol regulation in those with a psychiatric disorder could have significant physiologic consequences (McEwen 1998). Disturbances in cortisol secretion and regulation have been observed in a variety of psychiatric disorders, with the most widely reported and consistent finding being elevated basal cortisol concentrations and impaired suppression of cortisol agonists by glucocorticoid receptor agonists in patients with major depression, although there have been discrepancies in reports (Nelson and Davis 1997). These abnormalities appear to be a state rather than a trait marker of depression because they resolve when the depression resolves (Plotsky et al 1998).

Some reports in posttraumatic stress disorder (PTSD), the anxiety disorder resulting from exposure to a sudden, extreme, uncontrollable stressor (e.g., threat to one's life), show a pattern of cortisol opposite that generally seen in major depression. Specifically, lower concentrations of cortisol (in plasma or urine; Kanter et al 2001; Mason et al 1986; Thaller et al 1999; Yehuda et al 1990, 1995a) and an enhanced suppression by the glucocorticoid agonist dexamethasone (Grossman et al 1996; Yehuda et al 1995a) have been found in military veterans with combat-related PTSD. There has been a great deal of interest in these findings because of the implication that they reflect a difference in the "biology" of PTSD compared with major depression (Yehuda 2000); however, elevated (Gotovac et al 2003; Liberzon et al 1999; Pitman and Orr 1990) and similar (Baker et al 1999; Kosten et al 1990; Spivak et al 2003; Yehuda et al 1991, 1993) cortisol concentrations and no enhanced dexamethasone suppression (Thaller et al 1999) have also been observed in combat veterans with PTSD compared with control subjects.

Studies of cortisol regulation in combat veteran populations are complicated by high rates of substance abuse and psychotropic medication use (Jacobsen et al 2001) as well as many other factors that may make this population unique. A more limited number of studies have been conducted in patients with PTSD secondary to other traumas, and conflicting results have also been reported. Low cortisol concentrations have been found in non-treatment-seeking Holocaust survivors with chronic sustained PTSD symptoms (Yehuda et al 1995b) and mothers suffering from PTSD secondary to their children having cancer (Glover and Poland 2002), and enhanced cortisol suppression by dexamethasone has been observed in female adult survivors of childhood sexual abuse (Stein et al 1997). Elevated cortisol concentrations, however, have also been reported in female adult survivors of childhood sexual abuse (Lemieux and Coe 1995), men and women with mixed traumatic experiences (Atmaca et al 2002), children with PTSD (Carrion et al 2002), and survivors of either a fire or multivehicle car accident (Maes et al 1998). Similar baseline cortisol levels compared with control subjects have been reported in female patients with PTSD secondary to a variety of traumas (Coupland et al 2003; Rasmusson et al 2001), male and female subjects with PTSD 6 months after a motor vehicle accident (Hawk et al 2000), and male and female subjects with mixed traumas (Kellner et al 2002, 2003). There is also a report of no difference in cortisol levels of female children who have been the victims of abuse and control subjects (De Bellis et al 1999). Significantly higher rates of nonsuppression of cortisol by dexamethasone in male and female patients with PTSD have been reported (Atmaca et al 2002).

Therefore, the finding of low cortisol concentrations and enhanced suppression by dexamethasone in patients with PTSD is not a consistent finding across studies. Differences in the composition of the populations studied are likely to account for some of the discrepancy. For example, there may be differences in the prevalence of variables associated with the presence of

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PTSD that directly or indirectly contribute to low or enhanced suppression of cortisol. Factors that have been suggested include the presence of childhood trauma, a chronic course of the disease, or more severe symptoms (Yehuda 2002). It is not clear how these factors could contribute to differences in cortisol regulation, but differences in the length and intensity of stress exposure are likely to be important. Repeated stress exposure associated with early life trauma or a prolonged course of symptoms could produce a blunting of affective or physiologic responses to stress. Repeated stress exposure results in a habituation of cortisol responses to acute stress in many animal models of chronic stress, but baseline cortisol levels in chronically stressed animals tend to be elevated (Dallman 1993; Jaferi et al 2003). Other factors that might be associated with PTSD, that may vary across study populations, and that are known to significantly affect cortisol include ethnicity, body mass index (BMI), age, and gender (Ukkola et al 2001).

This study examined some of these possible contributing factors in a general outpatient population with PTSD and a control group matched for age, ethnicity, and gender. The study investigated the relationships between basal and postdexamethasone salivary cortisol concentrations and severity of PTSD symptoms, childhood abuse, and time since the trauma. This investigation differed from many previous studies in that participants 1) had experienced a variety of noncombat related traumatic experiences, 2) had low rates of prior psychopharmacological treatment, 3) had low rates of prior alcohol or substance abuse, 4) had acutely sought treatment for their symptoms, 5) were not receiving disability compensation for their symptoms, and 6) collected salivary samples in their home environments. We hypothesized that, despite these differences, we would observe lower cortisol concentrations and enhanced suppression by dexamethasone and that both lower cortisol and enhanced suppression would be related to the presence of childhood trauma, as has been proposed (Yehuda 2002). In addition, dissociation, anger, and affective lability were assessed in PTSD subjects because these symptoms have been hypothesized to relate directly or indirectly to traumatic experiences (Carlson 2000) and may be associated with salivary cortisol concentrations.

Methods and Materials

Subjects

The study was approved by the Human Subjects Review Committee of Stanford University and the Research and Development Committee of the Veterans Affairs, Palo Alto Health Care System, and written informed consent was obtained from all subjects. PTSD subjects were recruited with radio and print advertisements calling for participants in a study of a medication for the treatment of distressing symptoms following a traumatic event. All subjects responding to this advertisement who were eligible were invited to participate in a study of salivary cortisol. Of 49 subjects who consented to be assessed after being provided information about the study, 18 subjects with a primary diagnosis of PTSD determined by a full psychiatric interview and the Clinician Administered PTSD Scale (CAPS; Weathers 1999) were included. Subjects with a primary diagnosis of another Axis I disorder within 6 months of the screening visit (determined by history and the Mini International Neuropsychiatric Interview (MINI; Sheehan et al 1998) or with either a medical condition or a pharmacological therapy that might affect endocrine functioning (e.g., diabetes, polycystic ovaries, use of nasal glucocorticoids) were excluded. Among the 49 subjects who were assessed, the reasons for exclusion were the lack of a current diagnosis of PTSD as the primary disorder (n = 12), being on a prohibited medication or having an excluded medical disorder (n = 8), a decision by the subject to discontinue (n = 6), and failure to return for follow up (n = 5). Control subjects were recruited through print advertisements calling for individuals with no history of psychiatric illness interested in participating as control subjects in a study of stress hormones in saliva. From this pool of potential control subjects, control subjects were matched with PTSD subjects for age (± 5 years), race, and gender. Eighteen control subjects without a history of PTSD (determined by the CAPS) or other psychiatric illness (determined by history and the MINI) were included in the study. Dissociation, anger, and affective lability were assesses with the State-Trait Anger Expression Inventory (Spielberger 1994), the Posttraumatic Dissociation Scale (Carlson, unpublished data), the Affective Lability Scale, and the Impulsive Aggression Scale (Carlson, unpublished data).

All subjects were screened for the presence of alcohol or other substance abuse or dependence (assessed by the MINI) and histories of psychopharmacologic treatment. Subjects with abuse or dependence histories within the last 12 months were excluded from the study. Two PTSD subjects reported some lifetime history of alcohol or polysubstance dependence. Substance abuse histories from a year before the study were not available on four subjects. Of the 17 PTSD subjects, 9 (53%) reported no history of previous psychopharmacologic treatment and 13 (76%) had not taken a psychopharmacologic agent in the last 3 months. Of the four patients who had taken a psychopharmacologic agent in the last 3 months, one discontinued fluoxetine and valproic acid 5 weeks earlier, two discontinued low-dose amitriptyline (25 mg/day for migraine headaches) 2 weeks prior, and 1 discontinued sertraline and zolpidem 2 weeks before the collection of the salivary samples. With the exception of oral contraceptives and estrogen replacement, subjects were free of all other medications known to have significant central nervous system effects or influence cortisol, including topical nasal or pulmonary corticosteroid treatment (associated with adrenal suppression; Patel et al 2001). Three PTSD and three control subjects reported either oral contraceptives use or estrogen replacement therapy.

From the total population of 36 subjects, one control subject and one PTSD subject were dropped from the pre- and postdexamethasone analyses. The control subject dropped had both a missing baseline salivary sample and dexamethasone salivary concentrations below the detection limit. The PTSD subject, who reported taking herbal supplements for fatigue up to 2 weeks before the study, was dropped because her salivary cortisol concentrations indicated clinically significant adrenal insufficiency (8 AM cortisol = .01 μg/dL; 4 PM = .02 μg/dL; 10 PM = .009 μg/dL, with an area under the curve [AUC] 3 SD below the mean for the PTSD group). Herbal therapies have been associated with clinical evidence of adrenal insufficiency, presumably because of components with glucocorticoid activity (Chang et al 2001). One additional control subject was dropped from the postdexamethasone analyses because of dexamethasone concentrations below the detection limit.

Experimental Protocol

After screening, the rationale for the experiment and the importance of stress in regulating cortisol were explained to the subjects. They were given six labeled saliva collection devices (Salivette, Newton, North Carolina), a .5-mg dexamethasone tablet, and detailed written instructions to take home. They were instructed to collect the samples on 2 relatively stress-free days (e.g., Saturday and Sunday) and to avoid eating, drinking, or brushing their teeth for at least 15 min or exercise for at least 1 hour before sampling saliva. They were asked to refrain from alcohol and smoking completely on these 2 days if possible without distress, or, if they could not do so, not to smoke for 1 hour before the sampling. They were given logs to record any deviation from this protocol. None of the subjects included in the study reported a deviation from the protocol. Samples were collected at 8 AM, 4 PM, and 10 PM for two consecutive days, taking the .5 mg dexamethasone right after the 10 PM sample.

Cortisol Analyses

Cortisol concentrations were determined by an outside laboratory (Salimetrics; State College, Pennsylvania) using an enzyme-linked immunoassay with a matrix specific for saliva. The intraassay coefficient of variability (CV) is 5.7% and the interassay CV is 6.9%. The limit of sensitivity was .007 μg/dL. Two control patients had postdexamethasone salivary cortisol values that were below the level of sensitivity of the assay (post-4 PM and post-10 PM for one subject and all three time points for the other subject). For the analyses, values of .006 μg/dL were used for these five values.

Dexamethasone Analyses

Compliance with dexamethasone administration was determined by measuring post 8:00 AM salivary dexamethasone concentrations using an enzyme-linked immunosorbent dexamethasone assay (International Diagnostic Systems, St. Joseph, Michigan). This assay has a cross-reactivity of .12% for cortisol and .07% for 11-OH cortisol. Post dexamethasone samples were compared with their respective baseline 8 AM samples to compensate for variations in nonspecific binding. The assay sensitivity (2 SD above the assay blanks) was .01 μg/dL.

Statistical Analyses

Because the salivary cortisol and dexamethasone values were skewed, $\log_e$ transformations were used to achieve a normal distribution for statistical analyses. The nontransformed data are presented in the Figure 1. Data were analyzed by repeated measures analysis of variance for main effects of group (control vs. PTSD), time of day, and group by time interactions. Area under the curve (AUC) cortisol was determined from $\log_e$-transformed cortisol values using the trapezoidal method. Correlation analyses were calculated using Pearson Product–Moment correlation coefficient. Results were considered significant at the .05 level.

Results

Subject Characteristics

Of the 17 subjects with PTSD included in the analyses, 15 were women, 16 self-identified as Caucasian and 1 as Hispanic. Of the 17 control subjects, 15 were female, 15 self-identified as Caucasian, 1 as Hispanic, and 1 as Middle-Eastern (classified as Caucasian for matching). The mean age in years ± SE of the control subjects was 40.3 ± 3.3 (range 24–67) and PTSD was 40.2 ± 2.6 (range 19–64). The classifications of the criterion A traumas associated with symptoms in the PTSD subjects are presented in Table 1. Many patients had experienced more than one trauma that resulted in PTSD symptoms, with childhood sexual abuse being the most common, followed by witnessing a death (e.g., finding a significant other after a suicide). The mean time since the index trauma, the event to which the patient attributed their current PTSD symptoms (e.g., intrusive memories), was 13.5 ± 2.7 (SE) years (range .5–35 years). The mean CAPS score for the PTSD subjects was 71.0 ± 4.1 (SE). Of the PTSD subjects, 60% also met the criteria for current major depression (postdating onset of PTSD) by the structured assessment the MINI (MINI diagnoses not available for two patients), 53% an anxiety disorder other than PTSD (e.g., panic, social phobia), and one patient an eating disorder not otherwise specified (periodic binging without purging, no binging during measurement period, BMI 18.8). Three control subjects reported exposure to potentially traumatic events but only transient psychological distress.

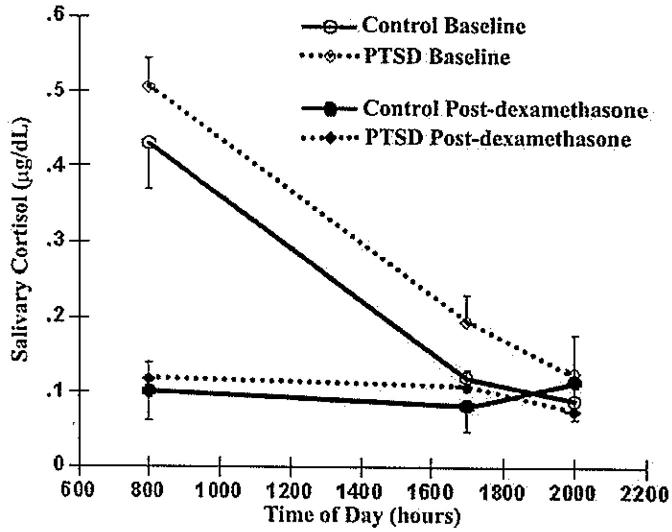

Figure 1. Salivary cortisol concentrations in control and posttraumatic stress disorder (PTSD) subjects collected the day before and the day after dexamethasone administration. Samples were collected by subjects at 8 AM, 4 PM, and 10 PM before and after administration of .5 mg dexamethasone at 10 PM. Salivary cortisol are expressed in mean μg/dL ± SE (n = 17). Log_e transformed data for control (C) versus PTSD (P) mean ± SE are for baseline 0800 (C −1.06 ± .19 vs. P −.83 ± .13), 1600 (C −2.25 ± .13 vs. P −1.88 ± .18), 2200 (C −2.66 ± .18 vs. P −2.26 ± .17) and postdexamethasone 8 AM (C −2.91 ± .28 vs. P −2.40 ± .18), 4 PM (C −3.30 ± .30 vs. P −2.62 ± .24), 10 PM (C −3.17 ± .35 vs. P −2.91 ± .20).

Salivary Cortisol Concentrations

A repeated-measures analysis of variance (ANOVA) of the transformed baseline salivary cortisol concentrations demonstrated a significant effect of group for PTSD versus control [$F(1,32) = 5.11, p < .05$] with higher concentrations in the PTSD group (see Figure 1 for the mean ± SE of untransformed data;

Table 1. Percent of Posttraumatic Stress Disorder subjects with symptoms attributed to a type of traumatic event

Type of Trauma	% of PTSD Subjects (n = 17)
Childhood Sexual Abuse	59
Witness to Violent Death	35
Childhood Physical Abuse	29
Serious Accident	24
Sexual Assault	18
Psychological Threat of Death	18
Adult Physical Assault	12

Some subjects reported symptoms from multiple types of trauma.

AUC 32.4% higher in the PTSD group). Analyses of the data without the four patients who had taken a psychopharmacologic agent in the last 3 months [$F(1,28) = 4.95$, $p < .05$] and without the six patients on estrogen or progesterone [$F(1,26) = 10.14$, $p < .05$] continued to demonstrate a significant effect of group with higher concentrations in the PTSD group. There was a significant decline in cortisol concentrations during the day in both groups, as indicated by a main effect for time of day [$F(2,64) = 52.06$, $p < .001$], but no significant group by time interaction. Post hoc analyses of the individual time points did not reveal any significant differences.

The concentrations of dexamethasone at 8 AM were not different between the two groups [Control = .063 ± .008 μg/dL, PTSD = .082 ± .016 μg/dL; $t(31) = 1.05$, *ns*], nor did they correlate with pre- or post dexamethasone cortisol concentrations (data not shown). Repeated-measures ANOVA of postdexamethasone salivary cortisol concentrations revealed no effect of group [$F(1,31) = 2.27$, *ns*] nor a group by time interaction [$F(1,31) = .86$, *ns*; Figure 1]. Analysis of postdexamethasone 8 AM cortisol alone also revealed no significant differences between the control and PTSD group [$t(31) = 1.58$, *ns*]. Because variations in either the levels of dexamethasone achieved or baseline cortisol concentrations could theoretically affect postdexamethasone values, postdexamethasone cortisol values were analyzed covarying for these factors. No significant effects were found for repeated-measures ANOVA of the three postdexamethasone cortisol values covarying for baseline 8 AM cortisol levels [$F(1,30) = 2.97$, *ns*] or dexamethasone levels [$F(1,30) = 2.14$, *ns*] nor for ANOVA of the postdexamethasone 8 AM cortisol alone covarying for baseline 8 AM cortisol [$F(1,30) = 2.22$, *ns*] or dexamethasone levels [$F(1,30) = 2.42$, *ns*].

Relation Among Salivary Cortisol and Gender, BMI, Age, and Ethnicity

Although the control groups were matched for gender, age, and ethnicity, because of the possible effect of these three variables and BMI on cortisol, the relation among these variables and salivary cortisol was examined. There was no significant difference in the BMI of the control [24.4 ± 1.4 (SE)] versus the PTSD [26.9 ± 2.0 (SE)] group and no significant correlation between BMI and AUC baseline ($r = .08$, *ns*) or postdexamethasone ($r = -.03$, *ns*) cortisol. There was no significant correlation between age and BMI ($r = .23$, *ns*), AUC baseline ($r = .04$, *ns*), or postdexamethasone ($r = .25$, *ns*) cortisol. Repeated-measures ANOVA of baseline salivary cortisol concentrations demonstrated no significant effects of gender [$F(1,32) = .96$, *ns*] or ethnicity [$F(2,31) = .89$, *ns*]. Likewise, there was no significant relationship between these variables and postdexamethasone salivary cortisol concentrations (data not shown).

Relation Among Salivary Cortisol, Childhood Abuse, Time since Trauma, PTSD Severity, and Major Depression

Comparing the PTSD subjects who had been the victims of childhood sexual or physical abuse (abuse before age 13, $n = 9$) with the PTSD subjects reporting no history of childhood sexual or physical abuse ($n = 8$) revealed no difference in CAPS scores (77.1 ± 5.8 vs. 64.1 ± 5.0) and baseline (4.0 ± .8 vs. 3.4 ± .5) or postdexamethasone (1.5 ± .3 vs. 1.4 ± .4) AUC cortisol. Comparing the PTSD subjects who were classified as having concurrent major depression by the MINI ($n = 9$) with those subjects without current major depression ($n = 6$) revealed no significant difference in CAPS scores (75.8 ± 5.8 vs. 67.7 ± 7.0) and baseline (4.6 ± 1.2 vs. 3.3 ± .4) or postdexamethasone (1.3 ± .4 vs. 1.4 ± .3) AUC cortisol. In the subjects with PTSD, the amount of time since the index trauma was positively correlated with their PTSD severity, as determine by CAPS scores ($r = .59$, $p < .05$), but neither the time since the index trauma nor age at the time of trauma significantly correlated with either baseline salivary cortisol or the magnitude of dexamethasone suppression. Salivary cortisol concentrations were not significantly correlated with CAPS scores.

Relation Among Salivary Cortisol, Anger, Affective Lability, and Dissociation

The CAPS scores were positively correlated with affective lability ($r = .65$, $p < .01$), self-directed impulsive aggression ($r = .61$, $p < .01$), other-directed impulsive aggression ($r = .68$, $p < .01$), and dissociation ($r = .71$, $p < .05$), but not with any index of anger. An index of the degree to which angry feelings are held in or suppressed was positively correlated with AUC baseline cortisol ($r = .57$, $p < .05$), but none of the other measures of anger, dissociation, or affective lability correlated with the salivary cortisol measurements.

Discussion

Contrary to expectations, the main findings of this study were that the sample of patients with PTSD had higher salivary cortisol concentrations than matched control subjects but similar rates of dexamethasone suppression. This finding is consistent with reports of elevated levels of cortisol concentrations (urinary or plasma) in male combat veterans (Liberzon et al 1999; Pitman and Orr 1990), adult female victims of childhood sexual abuse (Lemieux and Coe 1995a), men and women with mixed traumatic experiences (Atmaca et al 2002), children with PTSD (Carrion et al 2002), survivors of either a fire or a multivehicle car accident (Maes et al 1998), and men with recent-onset PTSD secondary to a motor vehicle accident (Hawk et al 2000). It is unclear why the samples of PTSD subjects in these studies showed elevated cortisol concentrations, but collectively the results indicate that low cortisol is not a trait marker of PTSD.

There were distinguishing characteristics in the current sample of patients compared with many other studies that may have contributed to the finding of elevated cortisol concentrations. For example, the subjects' recent decision to seek research medication treatment, many after years of chronic symptoms (mean 13.5 ± 11 years), may have been associated with increased psychologic distress and, therefore, with elevated cortisol levels. Cortisol concentrations over time in subjects with PTSD symptoms have been reported to be dynamic, possibly reflecting their fluctuating psychological states (Mason et al 2002). The majority of the subjects in the study had never received psychologic or psychopharmacologic therapies nor had they been diagnosed with PTSD before enrolling in the study. Conversely, this sample may have been relatively free of characteristics present in other samples that might lower cortisol concentrations. For example, there was a relatively low rate of previous substance abuse, with all the subjects reporting no history of abuse or dependence in the last year. Short-term abstinence (mean of 4 months) from alcohol dependence is associated with lower cortisol concentrations (Anthenelli et al 2001). Although it is unknown how being on financial disability for a psychiatric illness could affect one's level of emotional arousal and cortisol levels, this population did differ from many previously examined in that none of the subjects was on or applying for financial disability. Age, ethnicity, and gender can all affect cortisol (Ukkola et al 2001) and were controlled for in our study. It has been suggested that differences in gender among studies could contribute to the discrepancy in cortisol findings in PTSD (reviewed in Yehuda 2002). Our sample demonstrating elevated cortisol concentrations was 88% female, consistent with the findings of elevated cortisol concentration in the female patients studies by Lemieux and Coe and Maes and coworkers (Lemieux and Coe 1995; Maes et al 1998). Biological factors (e.g., estrogen) as well as numerous nonbiological factors (e.g., level of social support, aspects of the traumatic experience) could contribute to differences in cortisol responses in female versus male patients.

Enhanced negative feedback has been suggested to be a more consistent marker of PTSD than cortisol concentrations (Yehuda 2002). There was no significant difference in the cortisol responses to the glucocorticoid receptor agonist dexamethasone even after covarying for the higher baseline cortisol values in the PTSD group; however, there is evidence that salivary cortisol may be a less reliable measure for subtle differences in dexamethasone responses (Reynolds et al 1998).

A positive correlation was observed between the time passed since the index trauma and the severity of PTSD symptoms, as measured by the CAPS, indicating that the more chronic the illness, the more intense or frequent the symptoms of PTSD. There was no significant correlation, however, between the time passed since the index trauma and basal or dexamethasone-suppressed cortisol concentrations. Similarly, the presence or absence of childhood abuse did not significantly relate to cortisol concentrations. The childhood abuse findings are limited by the self-report nature of the reports. The severity of PTSD symptoms was also not significantly associated with basal cortisol concentrations; PTSD symptom severity has been positively (Smith et al 1989), negatively (Kellner et al 1997), and not correlated (Maes et al 1998) with baseline cortisol previously. Finally, measures of trauma-related symptoms including affective lability, dissociation, and aggression correlated with PTSD symptom severity but not with the cortisol measurements.

Although in this study we attempted to control many of the factors that could affect cortisol, we were not able to control all extraneous factors. These include past medication use, ovarian cycle phase, estrogen use, smoking, and diet. Preclinical data in animals suggest that psychotropic medications can affect cortisol regulation (Barden 1999; Pariante et al 2001), although their effects in a clinical population are not clear. If psychotropic medication use did affect cortisol, the most pronounced effect would presumably be observed in the 24% of the patients who had been taking psychotropic agents until 2 weeks before the sampling. Because analyses of the data without these four patients continued to demonstrate higher cortisol concentrations in the PTSD subjects, recent medication use did not appear to explain the finding of higher baseline cortisol concentrations in those with PTSD.

Neither the phase of the estrous cycle nor the use of oral contraceptives was controlled in this study. Cortisol binding globulin is significantly affected by estrogen, but basal salivary cortisol concentrations, which reflects nonbound cortisol, do not appear to vary across the estrous cycle (Groschl et al 2001; Kirschbaum et al 1999; McCormick and Teillon 2001) or with oral contraceptive use (Kirschbaum et al 1999; McCormick and Teillon 2001), although stress-induced changes in free cortisol are affected by both the phase of the estrous cycle and oral contraceptives (Kirschbaum et al 1999). As with prior medication use, analyses of the data without the patients on oral contraceptives or estrogen did not affect the main finding, indicating that these factors were not responsible for the main finding of higher baseline cortisol concentrations. Unfortunately, we did not assess menstrual cycle phase and were unable to investigate the possible influence of that factor. Theoretically, a sufficiently large, unequal distribution of the menstrual cycle phase that patients in the two groups were in could affect the results.

High levels of caffeine and nicotine can both increase cortisol concentrations (Kirschbaum et al 1997; Nickell and Uhde 1994), although patients in acute withdrawal from these agents also have altered levels of cortisol (Frederick et al 1998); it is therefore unclear how best to control for these factors. To prevent creating a nonrepresentative sample, we included smokers and caffeine users. We asked them to refrain from using cigarettes if possible to do so without significant distress or to restrict their use of cigarettes or caffeine beverages for 1 hour before sampling as a compromise between the possible acute effects and the effects of withdrawal. High protein diets and meals elevate salivary cortisol concentrations (Gibson et al 1999) and plasma glucose levels alter stressed-induced increases in cortisol (Kirschbaum et al 1997). Diet and food intake was not controlled in this study nor, to our knowledge, in any of the previous studies.

In conclusion, elevated levels of cortisol without a significant difference in the magnitude of suppression by dexamethasone were observed in subjects with PTSD presenting for treatment. Together with previous findings, our findings indicate that neither low basal concentrations nor enhanced dexamethasone suppression is a consistent marker of a PTSD diagnosis. Given the potential ability of cortisol to induce pathology if abnormally attenuated or stimulated for prolonged periods of time, longitudinal investigations of diverse populations of patients are needed to determine which factors might expose PTSD patients to either prolonged hypo- or hypercortisolism.

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Anthenelli RM, Maxwell RA, Geracioti TD Jr, Hauger R (2001): Stress hormone dysregulation at rest and after serotonergic stimulation among alcohol-dependent men with extended abstinence and controls. *Alcohol Clin Exp Res* 25:692–703.

Atmaca M, Kuloglu M, Tezcan E, Onal S, Ustundag B (2002): Neopterin levels and dexamethasone suppression test in posttraumatic stress disorder. *Eur Arch Psychiatry Clin Neurosci* 252:161–165.

Baker DG, West SA, Nicholson WE, Ekhator NN, Kasckow JW, Hill KK, et al (1999): Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. *Am J Psychiatry* 156:585–588.

Barden N (1999): Regulation of corticosteroid receptor gene expression in depression and antidepressant action. *J Psychiatry Neurosci* 24:25–39.

Carlson EB, Dalenberg C (2000): A conceptual framework for the impact of traumatic experiences. *Traum Violence Abuse* 1:4–28.

Carrion VG, Weems CF, Ray RD, Glaser B, Hessl D, Reiss AL (2002): Diurnal salivary cortisol in pediatric posttraumatic stress disorder. *Biol Psychiatry* 51:575–82.

Chang SS, Liaw SJ, Bullard MJ, Chiu TF, Chen JC, Liao HC (2001): Adrenal insufficiency in critically ill emergency department patients: A Taiwan preliminary study. *Acad Emerg Med* 8:761–764.

Coupland NJ, Hegadoren KM, Myrholm J (2003): Increased beclomethasone-induced vasoconstriction in women with posttraumatic stress disorder. *J Psychiatr Res* 37:221–228.

Dallman MF (1993): Stress update: Adaptation of the hypothalamic-pituitary-adrenal axis to chronic stress. *Trends Endocrinol Metab* 4:62–69.

De Bellis MD, Baum AS, Birmaher B, Keshavan MS, Eccard CH, Boring AM, et al (1999): A.E. Bennett Research Award. Developmental traumatology. Part I: Biological stress systems. *Biol Psychiatry* 45:1259–1270.
Frederick SL, Reus VI, Ginsberg D, Hall SM, Munoz RF, Ellman G (1998): Cortisol and response to dexamethasone as predictors of withdrawal distress and abstinence success in smokers. *Biol Psychiatry* 43:525–530.
Gibson EL, Checkley S, Papadopoulos A, Poon L, Daley S, Wardle J (1999): Increased salivary cortisol reliably induced by a protein-rich midday meal. *Psychosom Med* 61:214–224.
Glover DA, Poland RE (2002): Urinary cortisol and catecholamines in mothers of child cancer survivors with and without PTSD. *Psychoneuroendocrinology* 27:805–819.
Gotovac K, Sabioncello A, Rabatic S, Berki T, Dekaris D (2003): Flow cytometric determination of glucocorticoid receptor (GCR) expression in lymphocyte subpopulations: Lower quantity of GCR in patients with posttraumatic stress disorder (PTSD). *Clin Exp Immunol* 131:335–339.
Groschl M, Rauh M, Schmid P, Dorr HG (2001): Relationship between salivary progesterone, 17-hydroxyprogesterone, and cortisol levels throughout the normal menstrual cycle of healthy postmenarcheal girls. *Fertil Steril* 76:615–617.
Grossman R, Yehuda R, Boisoneau D, Schmeidler J, Giller EL Jr (1996): Prolactin response to low-dose dexamethasone challenge in combat-exposed veterans with and without posttraumatic stress disorder and normal controls. *Biol Psychiatry* 40:1100–1105.
Hawk LW, Dougall AL, Ursano RJ, Baum A (2000): Urinary catecholamines and cortisol in recent-onset posttraumatic stress disorder after motor vehicle accidents. *Psychosom Med* 62:423–434.
Jacobsen LK, Southwick SM, Kosten TR (2001): Substance use disorders in patients with posttraumatic stress disorder: A review of the literature. *Am J Psychiatry* 158:1184–1190.
Jaferi A, Nowak N, Bhatnagar S (2003): Negative feedback functions in chronically stressed rats: Role of the posterior paraventricular thalamus. *Physiol Behav* 78:365–373.
Kanter ED, Wilkinson CW, Radant AD, Petrie EC, Dobie DJ, McFall ME, et al (2001): Glucocorticoid feedback sensitivity and adrenocortical responsiveness in posttraumatic stress disorder. *Biol Psychiatry* 50:238–245.
Kellner M, Baker DG, Yassouridis A, Bettinger S, Otte C, Naber D, et al (2002): Mineralocorticoid receptor function in patients with posttraumatic stress disorder. *Am J Psychiatry* 159:1938–1940.
Kellner M, Baker DG, Yehuda R (1997): Salivary cortisol in Operation Desert Storm returnees. *Biol Psychiatry* 42:849–850.
Kellner M, Yassouridis A, Hubner R, Baker DG, Wiedemann K (2003): Endocrine and cardiovascular responses to corticotropin-releasing hormone in patients with posttraumatic stress disorder: A role for atrial natriuretic peptide? *Neuropsychobiology* 47:102–108.
Kirschbaum C, Gonzalez Bono E, Rohleder N, Gessner C, Pirke KM, Salvador A, et al (1997): Effects of fasting and glucose load on free cortisol responses to stress and nicotine. *J Clin Endocrinol Metab* 82:1101–1105.
Kirschbaum C, Kudielka BM, Gaab J, Schommer NC, Hellhammer DH (1999): Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamus-pituitary-adrenal axis. *Psychosom Med* 61:154–162.
Kosten TR, Wahby V, Giller E Jr, Mason J (1990): The dexamethasone suppression test and thyrotropin-releasing hormone stimulation test in posttraumatic stress disorder. *Biol Psychiatry* 28:657–664.
Lemieux AM, Coe CL (1995): Abuse-related posttraumatic stress disorder: Evidence for chronic neuroendocrine activation in women. *Psychosom Med* 57:105–115.
Liberzon I, Abelson JL, Flagel SB, Raz J, Young EA (1999): Neuroendocrine and psychophysiologic responses in PTSD: A symptom provocation study. *Neuropsychopharmacology* 21:40–50.
Maes M, Lin A, Bonaccorso S, van Hunsel F, Van Gastel A, Delmeire L, et al (1998): Increased 24-hour urinary cortisol excretion in patients with post-traumatic stress disorder and patients with major depression, but not in patients with fibromyalgia. *Acta Psychiatr Scand* 98:328–335.
Mason JW, Giller EL, Kosten TR, Ostroff RB, Podd L (1986): Urinary free-cortisol levels in posttraumatic stress disorder patients. *J Nerv Ment Dis* 174:145–149.
Mason JW, Wang S, Yehuda R, Lubin H, Johnson D, Bremner JD, et al (2002): Marked lability in urinary cortisol levels in subgroups of combat veterans with posttraumatic stress disorder during an intensive exposure treatment program. *Psychosom Med* 64:238–246.
McCormick CM, Teillon SM (2001): Menstrual cycle variation in spatial ability: Relation to salivary cortisol levels. *Horm Behav* 39:29–38.
McEwen BS (1998): Protective and damaging effects of stress mediators. *N Engl J Med* 338:171–179.
Nelson JC, Davis JM (1997): DST studies in psychotic depression: A meta-analysis. *Am J Psychiatry* 154:1497–1503.
Nickell PV, Uhde TW (1994): Dose-response effects of intravenous caffeine in normal volunteers. *Anxiety* 1:161–168.
Pariante CM, Makoff A, Lovestone S, Feroli S, Heyden A, Miller AH, et al (2001): Antidepressants enhance glucocorticoid receptor function in vitro by modulating the membrane steroid transporters. *Br J Pharmacol* 134:1335–1343.
Patel RS, Wallace AM, Hinnie J, McGarry GW (2001): Preliminary results of a pilot study investigating the potential of salivary cortisol measurements to detect occult adrenal suppression secondary to steroid nose drops. *Clin Otolaryngol* 26:231–234.
Pitman RK, Orr SP (1990): Twenty-four hour urinary cortisol and catecholamine excretion in combat-related posttraumatic stress disorder. *Biol Psychiatry* 27:245–247.
Plotsky PM, Owens MJ, Nemeroff CB (1998): Psychoneuroendocrinology of depression; hypothalamic-pituitary-adrenal axis. *Psychiatr Clin North Am* 21:293–307.
Rasmusson AM, Lipschitz DS, Wang S, Hu S, Vojvoda D, Bremner JD, et al (2001): Increased pituitary and adrenal reactivity in premenopausal women with posttraumatic stress disorder. *Biol Psychiatry* 50:965–977.
Reynolds RM, Bendall HE, Whorwood CB, Wood PJ, Walker BR, Phillips DI (1998): Reproducibility of the low dose dexamethasone test: Comparison between direct plasma and salivary cortisol assays. *Clin Endocrin* 49:307–310.
Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al (1998): The Mini-International Neuropsychiatric Interview (MINI): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 59:22–33.
Smith MA, Davidson J, Ritchie JC, Kudler H, Lipper S, Chappell P, et al (1989): The corticotropin-releasing hormone test in patients with posttraumatic stress disorder. *Biol Psychiatry* 26:349–355.
Spielberger CD, Syndemna, Sumner, J (1994): *State-Trait Anxiety Inventory and StateTrait Expression Inventory*, vol. XV. Hillsdale, NJ: Erlbaum.
Spivak B, Maayan R, Mester R, Weizman A (2003): Plasma testosterone levels in patients with combat-related posttraumatic stress disorder. *Neuropsychobiology* 47:57–60.
Stein MB, Yehuda R, Koverola C, Hanna C (1997): Enhanced dexamethasone suppression of plasma cortisol in adult women traumatized by childhood sexual abuse. *Biol Psychiatry* 42:680–686.
Thaller V, Vrkljan M, Hotujac L, Thakore J (1999): The potential role of hypocortisolism in the pathophysiology of PTSD and psoriasis. *Coll Antropol* 23:611–619.
Ukkola O, Gagnon J, Rankinen T, Thompson PA, Hong Y, Leon AS, et al (2001): Age, body mass index, race and other determinants of steroid hormone variability: The HERITAGE Family Study. *Eur J Endocrinol* 145:1–9.
Weathers FW, Ruscio AM, Keane TM (1999): Psychometric properties of nine scoring rules for the Clinician-Administered Posttraumatic Stress Disorder Scale. *Psychol Assess* 11:124–133.
Yehuda R (2000): Biology of posttraumatic stress disorder. *J Clin Psychiatry* 61(suppl 7):14–21.
Yehuda R (2002): Current status of cortisol findings in post-traumatic stress disorder. *Psychiatr Clin North Am* 25:341–368.
Yehuda R, Boisoneau D, Lowy MT, Giller EL Jr (1995a): Dose-response changes in plasma cortisol and lymphocyte glucocorticoid receptors following dexamethasone administration in combat veterans with and without posttraumatic stress disorder. *Arch Gen Psychiatry* 52:583–593.
Yehuda R, Kahana B, Binder-Brynes K, Southwick SM, Mason JW, Giller EL (1995b): Low urinary cortisol excretion in Holocaust survivors with posttraumatic stress disorder. *Am J Psychiatry* 152:982–986.
Yehuda R, Lowy MT, Southwick SM, Shaffer D, Giller EL Jr (1991): Lymphocyte glucocorticoid receptor number in posttraumatic stress disorder. *Am J Psychiatry* 148:499–504.
Yehuda R, Southwick SM, Krystal JH, Bremner D, Charney DS, Mason JW (1993): Enhanced suppression of cortisol following dexamethasone administration in posttraumatic stress disorder. *Am J Psychiatry* 150:83–86.
Yehuda R, Southwick SM, Nussbaum G, Wahby V, Giller EL Jr, Mason JW (1990): Low urinary cortisol excretion in patients with posttraumatic stress disorder. *J Nerv Ment Dis* 178:366–369.